PREVACID NAPRAPAC - lansoprazole and naproxen
Takeda Pharmaceuticals America, Inc.

Rx only

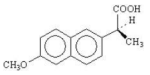
Cardiovascular Risk
- **NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).**
- **PREVACID NapraPAC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).**

Gastrointestinal (GI) Risk
- **NSAIDs cause an increased risk of serious GI adverse events including bleeding and perforation of the stomach and intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Patients with a history of gastric and/or duodenal ulcers (especially patients with a history of bleeding or perforation) and geriatric patients are at greater risk for serious GI events (see WARNINGS and CLINICAL STUDIES, Risk Reduction of NSAID-Associated Gastric Ulcer(s)).**

PREVACID® NapraPAC® 500 is a combination package containing two individual drug products: PREVACID® (lansoprazole) Delayed-Release Capsules, a proton pump inhibitor (PPI), and NAPROSYN® (naproxen tablets), a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The information described in this labeling concerns only the use of these products as indicated in this combination package and does not include all individual use information. For information on use of the components when dispensed as individual medications outside this combination package, please see the package inserts for PREVACID Delayed-Release Capsules and NAPROSYN Tablets.

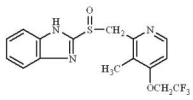
DESCRIPTION
PREVACID NapraPAC 500 is a combination package containing NAPROSYN 500 mg tablets and PREVACID 15 mg capsules.

NAPROSYN
Naproxen is a proprionic acid derivative related to the arylacetic acid group of NSAIDs. The chemical name for naproxen is (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid and naproxen has the following structure:



Naproxen has a molecular weight of 230.26 and a molecular formula of $C_{14}H_{14}O_3$.
Naproxen is an odorless, white to off-white crystalline substance. It is lipid-soluble, practically insoluble in water at low pH and freely soluble in water at high pH. The octanol/water partition coefficient of naproxen at pH 7.4 is 1.6 to 1.8.
NAPROSYN (naproxen tablets) is available as yellow tablets containing 500 mg of naproxen for oral administration. The inactive ingredients are croscarmellose sodium, iron oxides, povidone, and magnesium stearate.

PREVACID
The active ingredient in PREVACID Delayed-Release capsules is lansoprazole, a substituted benzimidazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_3O_2S$ with a molecular weight of 369.37. PREVACID has the following structure:



Lansoprazole is a white to brownish-white odorless crystalline powder which melts with decomposition at approximately 166°C. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol; sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile; very slightly soluble in ether; and practically insoluble in hexane and water.
Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5 and approximately 18 hours at pH 7.
PREVACID Delayed-Release capsules contain enteric-coated granules consisting of 15 mg of lansoprazole (active ingredient) and the following inactive ingredients: sugar sphere, sucrose, methacrylic acid copolymer, low substituted hydroxypropyl cellulose, starch,

magnesium carbonate, talc, polyethylene glycol, titanium dioxide, polysorbate 80, hydroxypropyl cellulose, colloidal silicon dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3, and FD&C Red No. 40.

CLINICAL PHARMACOLOGY

Pharmacokinetics

NAPROSYN

Absorption
Naproxen is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. After administration of NAPROSYN tablets, peak plasma levels are attained in 2 to 4 hours. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life.

Distribution
Naproxen has a volume of distribution of 0.16 L per kg. At therapeutic levels, naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg per day, there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough concentrations at steady state were 36.5, 49.2 and 56.4 mg per L with 500, 1000, and 1500 mg daily doses of naproxen, respectively).

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of the maximum naproxen concentration in plasma (see **PRECAUTIONS, Nursing Mothers**).

Metabolism
Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-0-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Excretion
The clearance of naproxen is 0.13 mL per min per kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen disappearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate (see **WARNINGS, Renal Effects**).

Special Populations

Pediatric Patients
The combination of naproxen and lansoprazole has not been studied in pediatric patients (see **CLINICAL PHARMACOLOGY, PREVACID Special Populations – Pediatric Use**).

Geriatric Patients
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is less than 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear; although, it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients.

Race
Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency
Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency.

Renal Insufficiency
Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency (see **CLINICAL PHARMACOLOGY, PREVACID Special Populations - Renal Insufficiency**). Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen-containing products are not recommended for use in

patients with moderate to severe and severe renal impairment – (creatinine clearance less than 30 mL per min – see **WARNINGS, Renal Effects**).

PREVACID

PREVACID Delayed-Release capsules contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak plasma concentrations (C_{max}) of lansoprazole and the area under the plasma concentration curves (AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with the mean C_{max} occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (± SD) plasma half-life was 1.5 (± 1.0) hours. Both the C_{max} and AUC are diminished by about 50 to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5 mcg per mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H^+,K^+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination

Following single-dose oral administration of PREVACID, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Special Populations

Pediatric Use

The combination of lansoprazole and naproxen has not been studied in pediatric patients (see **CLINICAL PHARMACOLOGY, NAPROSYN Special Populations – Pediatric Use**).

Geriatric Use

The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Because the mean half-life in the elderly remains between 1.9 to 2.9 hours, repeated once daily dosing does not result in accumulation of lansoprazole. Peak plasma levels were not increased in the elderly.

Gender

In a study comparing 12 male and 6 female human subjects who received lansoprazole, no gender differences were found in pharmacokinetics and intragastric pH results (see **PRECAUTIONS, PREVACID Use in Women**).

Renal Insufficiency

In patients with severe renal insufficiency, plasma protein binding decreased by 1% to 1.5% after administration of 60 mg of lansoprazole. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound). The AUC for free lansoprazole in plasma, however, was not related to the degree of renal impairment; and the C_{max} and T_{max} (time to reach the maximum concentration) were not different than the C_{max} and T_{max} from subjects with normal renal function (see **CLINICAL PHARMACOLOGY, NAPROSYN Special Populations - Renal Insufficiency**).

Hepatic Insufficiency

In patients with various degrees of chronic hepatic disease, the mean plasma half-life of lansoprazole was prolonged from 1.5 hours to 3.2 to 7.2 hours. An increase in the mean AUC of up to 500% was observed at steady state in hepatically-impaired patients compared to healthy subjects. Dose reduction in patients with severe hepatic disease should be considered.

Race
The pooled mean pharmacokinetic parameters of PREVACID from twelve U.S. Phase I studies (N=513) were compared to the mean pharmacokinetic parameters from two Asian studies (N=20). The mean AUCs of PREVACID in Asian subjects were approximately twice that seen in pooled U.S. data; however, the inter-individual variability was high. The C_{max} values were comparable.

Pharmacodynamics

NAPROSYN
Naproxen is a NSAID with analgesic and antipyretic properties. The mechanism of action of the naproxen anion, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

PREVACID

Mechanism of Action
PREVACID (lansoprazole) belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

Antisecretory Activity
After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was greater than 3 and greater than 4. Lansoprazole also significantly reduced meal-stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. Lansoprazole inhibited the normal increases in secretion volume, acidity and acid output induced by insulin.

The intragastric pH results of a five-day, pharmacodynamic, crossover study of 15 mg and 30 mg of once daily lansoprazole are presented in Table 1.

Table 1: Mean Antisecretory Effects after single and multiple daily PREVACID dosing

		PREVACID			
	Baseline Value	**15 mg**		**30 mg**	
Parameter		**Day 1**	**Day 5**	**Day 1**	**Day 5**
Mean 24-Hour pH	2.1	2.7*	4.0*	3.6†	4.9†
Mean Nighttime pH	1.9	2.4	3.0*	2.6	3.8†
% Time Gastric pH>3	18	33*	59*	51†	72†
% Time Gastric pH>4	12	22*	49*	41†	66†

NOTE: An intragastric pH of greater than 4 reflects a reduction in gastric acid by 99%.
*****($p<0.05$) versus baseline only.
†($p<0.05$) versus baseline and lansoprazole 15 mg.

After the initial dose in this study, increased gastric pH was seen within 1 to 2 hours with 30 mg of lansoprazole and 2 to 3 hours with 15 mg of lansoprazole. After multiple daily dosing, increased gastric pH was seen within the first hour post-dosing with 30 mg of lansoprazole and within 1 to 2 hours post-dosing with 15 mg of lansoprazole.

The inhibition of gastric acid secretion as measured by intragastric pH gradually returned to normal over two to four days after multiple doses. There was no indication of rebound gastric acidity.

Enterochromaffin-like (ECL) Cell Effects
During lifetime exposure of rats with up to 150 mg per kg per day of lansoprazole dosed seven days per week, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats (see **PRECAUTIONS, PREVACID Carcinogenesis, Mutagenesis, Impairment of Fertility**).

Gastric biopsy specimens from the body of the stomach from approximately 150 patients treated continuously with lansoprazole for at least one year did not show evidence of ECL cell effects similar to those seen in rat studies. Longer term data are needed to rule out the possibility of an increased risk of the development of gastric tumors in patients receiving long-term therapy with lansoprazole.

Other Gastric Effects in Humans
Lansoprazole did not significantly affect mucosal blood flow in the fundus of the stomach. Due to the normal physiologic effect caused by the inhibition of gastric acid secretion, a decrease of about 17% in blood flow in the antrum, pylorus, and duodenal bulb was seen. Lansoprazole significantly slowed the gastric emptying of digestible solids. Lansoprazole increased serum pepsinogen levels and decreased pepsin activity under basal conditions and in response to meal stimulation or insulin injection. As with other agents that elevate intragastric pH, increases in gastric pH were associated with increases in nitrate-reducing bacteria and elevation of nitrite concentration in gastric juice in patients with gastric ulcer. No significant increase in nitrosamine concentrations was observed.

Serum Gastrin Effects
In over 2100 patients, median fasting serum gastrin levels increased 50% to 100% from baseline but remained within normal range after treatment with 15 to 60 mg of oral lansoprazole. These elevations reached a plateau within two months of therapy and returned to pretreatment levels within four weeks after discontinuation of therapy.

Endocrine Effects
Human studies for up to one year have not detected any clinically significant effects on the endocrine system. Hormones studied include testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), prolactin, cortisol, estradiol, insulin, aldosterone, parathormone, glucagon, thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), and somatotropic hormone (STH). Lansoprazole in oral doses of 15 to 60 mg for up to one year had no clinically significant effect on sexual function. In addition, lansoprazole in oral doses of 15 to 60 mg for two to eight weeks had no clinically significant effect on thyroid function.

In 24-month carcinogenicity studies in Sprague-Dawley rats with daily lansoprazole dosages up to 150 mg per kg, proliferative changes in the Leydig cells of the testes, including benign neoplasm, were increased compared to control rates.

Other Effects
No systemic effects of lansoprazole on the central nervous system, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems have been found in humans. Among 56 patients who had extensive baseline eye evaluations, no visual toxicity was observed after lansoprazole treatment (up to 180 mg per day) for up to 58 months.

After lifetime lansoprazole exposure in rats, focal pancreatic atrophy, diffuse lymphoid hyperplasia in the thymus, and spontaneous retinal atrophy were seen.

CLINICAL STUDIES

Risk Reduction of NSAID-Associated Gastric Ulcer(s)
A large U.S., multicenter, double-blind, placebo- and misoprostol-controlled (misoprostol blinded only to the endoscopist) 12-week study was conducted in patients who required chronic use of an NSAID and had a history of an endoscopically documented gastric ulcer. Patients were randomized to one of the following four treatment groups: PREVACID 15 mg per day, PREVACID 30 mg per day, misoprostol 200 micrograms QID, and placebo. Patients were allowed to take one or more NSAIDs and take concomitant low-dose aspirin (≤ 325 mg per day) during the study. Patients who had gastric ulcers, duodenal ulcers, erosive esophagitis, or ≥25 gastric/duodenal erosions on baseline upper endoscopy were excluded from participation. Patients had to be *H. pylori* negative by the CLO test and by histology testing.
A total of 537 patients were enrolled in the study, and 535 patients were treated. Patients ranged in age from 23 to 89 years (median age 60 years), with 65% female patients and 35% male patients. Race was distributed as follows: 90% Caucasian, 6% Black, and 4% other. Concomitant low-dose aspirin was used in about 20% of the patients. Additionally, about 99% of the patients had a prior history of a gastric ulcer and about 50% of the patients had a prior history of a duodenal ulcer.
The proportion of patients remaining free from gastric ulcers (diagnosed by upper endoscopy) at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of PREVACID than placebo (see Table 2). The 30 mg dose of PREVACID demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcer(s) than the 15 mg dose. In the 12 week study, no patient in any of the treatment groups developed a NSAID-associated serious GI complication (such as bleeding, perforation, or obstruction). However, this study was not designed to demonstrate risk reduction of NSAID-associated serious GI complications. Additionally, this study was not designed to demonstrate risk reduction of duodenal ulcers.

Table 2: Proportion of Patients Remaining Free of Gastric Ulcers*

Week	PREVACID 15 mg daily (N=121)	PREVACID 30 mg daily (N=116)	Misoprostol 200 mcg QID (N=106)	Placebo (N=112)
4	90%	92%	96%	66%
8	86%	88%	95%	60%
12	80%	82%	93%	51%

(p<0.001) PREVACID 15 mg daily versus placebo; PREVACID 30 mg daily versus placebo; and misoprostol 200 mcg QID versus placebo.

(p<0.05) Misoprostol 200 mcg QID versus PREVACID 15 mg daily; and misoprostol 200 mcg QID versus PREVACID 30 mg daily

*****% = Life Table Estimate

Of the 537 patients in the double-blind, placebo- and misoprostol-controlled study, a retrospective subset analysis of 119 patients – whose NSAIDs were naproxen or naproxen and aspirin – was performed. Patients ranged in age from 37 to 84 years (median age 58 years) with 61% female patients and 39% male patients. Race was distributed as follows: 88% Caucasian, 8% Black, and 4% other. Concomitant low-dose aspirin was used in 15% of the patients. Of the 61 patients in the two PREVACID treatment groups: 5, 54, and 2 patients received less than 750 mg, 750 to 1000 mg, and greater than 1000 mg of daily naproxen, respectively.
The proportion of patients remaining free from gastric ulcer (diagnosed by upper endoscopy) at 4, 8, and 12 weeks was significantly higher with 15 or 30 mg of PREVACID than placebo (see Table 3). The 30 mg dose of PREVACID demonstrated no additional benefit in risk reduction of the NSAID-associated gastric ulcers than the 15 mg dose.

Table 3: Proportion of Patients (whose NSAIDs were Naproxen or Naproxen and Aspirin) Remaining Free of Gastric Ulcers[*]

Week	PREVACID 15 mg daily (N=37)	PREVACID 30 mg daily (N=24)	Misoprostol 200 mcg QID (N=28)	Placebo (N=30)
4	91%	83%	88%	52%
8	89%	83%	88%	52%
12	89%	83%	83%	33%

(p<0.001) PREVACID 15 mg daily versus placebo; PREVACID 30 mg daily versus placebo; and misoprostol 200 mcg QID versus placebo.
*****% = Life Table Estimate

NAPROSYN

General Information
Naproxen has been studied in patients with rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Improvement in patients treated for rheumatoid arthritis was demonstrated by a reduction in joint swelling, a reduction in duration of morning stiffness, a reduction in disease activity as assessed by both the investigator and patient, and by increased mobility as demonstrated by a reduction in walking time. Generally, response to naproxen has not been found to be dependent on age, sex, severity, or duration of rheumatoid arthritis.

In patients with osteoarthritis, the therapeutic action of naproxen has been shown by a reduction in joint pain or tenderness, an increase in range of motion in knee joints, increased mobility as demonstrated by a reduction in walking time, and improvement in capacity to perform activities of daily living impaired by the disease.

In a clinical trial comparing standard formulations of naproxen 375 mg bid (750 mg a day) vs 750 mg twice daily (1500 mg per day), 9 patients in the 750 mg group terminated prematurely because of adverse events. Nineteen patients in the 1500 mg group terminated prematurely because of adverse events. Most of these adverse events were GI events.

In clinical studies in patients with rheumatoid arthritis or osteoarthritis, naproxen has been shown to be comparable to aspirin and indomethacin in controlling the aforementioned measures of disease activity, but the frequency and severity of the milder GI adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less in naproxen-treated patients than in those treated with aspirin or indomethacin.

In patients with ankylosing spondylitis, naproxen has been shown to decrease night pain, morning stiffness and pain at rest. In double-blind studies the drug was shown to be as effective as aspirin, but with fewer side effects.

Naproxen may be used safely in combination with gold salts and/or corticosteroids; however, in controlled clinical trials, when added to the regimen of patients receiving corticosteroids, it did not appear to cause greater improvement over that seen with corticosteroids alone. Whether naproxen has a "steroid-sparing" effect has not been adequately studied. When added to the regimen of patients receiving gold salts, naproxen did result in greater improvement. Its use in combination with salicylates is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs, the combination may result in higher frequency of adverse events than demonstrated for either product alone.

In ^{51}Cr blood loss and gastroscopy studies with normal volunteers, daily administration of 1000 mg of naproxen as 1000 mg of NAPROSYN (naproxen) has been demonstrated to cause statistically significantly less gastric bleeding and erosion than 3250 mg of aspirin.

Geriatric Patients
The hepatic and renal tolerability of long-term naproxen administration was studied in two double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

INDICATIONS AND USAGE
Carefully consider the potential benefits and risks of PREVACID NapraPAC and other treatment options before deciding to use PREVACID NapraPAC. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).
PREVACID NapraPAC is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of documented gastric ulcer(s) who require the use of an NSAID for treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and/or ankylosing spondylitis (see **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**). Controlled studies did not extend beyond 12 weeks.

CONTRAINDICATIONS
PREVACID NapraPAC is contraindicated in patients with known severe hypersensitivity to any component of the formulations of PREVACID (lansoprazole), NAPROSYN (naproxen), or the over-the-counter products containing naproxen.
PREVACID NapraPAC is contraindicated in patients who have experienced aspirin- or NSAID-related asthma, urticaria, or allergic-type reactions. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see **WARNINGS, Anaphylactoid Reactions,** and **PRECAUTIONS –Preexisting Asthma**).
PREVACID NapraPAC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

CARDIOVASCULAR EFFECTS

Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see **GI WARNINGS** and **CLINICAL STUDIES, Risk Reduction of NSAID-Associated Gastric Ulcer(s)**).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see **CONTRAINDICATIONS**).

Hypertension
NSAIDs, including NAPROSYN, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including NAPROSYN, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention, edema, and peripheral edema have been observed in some patients taking NSAIDs. NAPROSYN should be used with caution in patients with fluid retention, hypertension, or heart failure.

GI Effects - Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including NAPROSYN, can cause serious GI adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal.

These serious adverse events can occur at any time, with or without warning symptoms in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only 1 in 5 patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or GI bleeding. Patients with a prior history of peptic ulcer disease and/or GI bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population. To minimize the potential risk for an adverse GI event in patients treated with PREVACID NapraPAC, the lowest effective NAPROSYN dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of PREVACID NapraPAC until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

For patients who require the use of NAPROSYN, coadministration with 15 mg of PREVACID Delayed-Release Capsules has been proven effective to reduce the risk of NSAID-associated gastric ulcers in patients with a previous history of documented gastric ulcer(s) (see **CLINICAL STUDIES, Risk Reduction of NSAID-Associated Gastric Ulcer(s)**).

Epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper GI bleeding. In two studies, concurrent use of an NSAID or aspirin potentiated the risk of bleeding (see **PRECAUTIONS: Drug Interactions**). Although these studies focused on upper GI bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated.

NSAIDs should be given with care to patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics, and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state (see **WARNINGS, Advanced Renal Disease**).

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of NAPROSYN in patients with advanced renal disease. Therefore, treatment with NAPROSYN is not recommended in these patients with advanced renal disease. If NAPROSYN therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to NAPROSYN and/or PREVACID. NAPROSYN should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS, Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Skin Reactions

NSAIDs, including NAPROSYN, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAIDs, NAPROSYN should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

NAPROSYN
Naproxen-containing products such as NAPROSYN, EC-NAPROSYN, ANAPROX, ANAPROX DS, NAPROSYN SUSPENSION, ALEVE®, and other naproxen products, including PREVACID NapraPAC, should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

NAPROSYN cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically.

The pharmacological activity of NAPROSYN in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including NAPROSYN. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions (including jaundice, and fatal fulminant hepatitis, liver necrosis, and hepatic failure), some of them with fatal outcomes, have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with NAPROSYN.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), NAPROSYN should be discontinued.

Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including NAPROSYN. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including NAPROSYN, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving NAPROSYN who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, NAPROSYN should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

PREVACID
Symptomatic response to therapy with lansoprazole does not preclude the presence of gastric malignancy.

Information for Patients
Each package of PREVACID NapraPAC contains sufficient product for seven days of treatment. Each daily dose consists of one PREVACID 15 mg capsule and two NAPROSYN tablets, 500 mg. In the morning before eating, take the PREVACID capsule and one NAPROSYN tablet with a glass of water. In the evening, take the second NAPROSYN tablet with a glass of water.
Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the PREVACID NapraPAC Medication Guide that accompanies each prescription dispensed.
1. NAPROSYN, like other NSAIDs, may cause serious cardiovascular (CV) side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see **WARNINGS, CARDIOVASCULAR EFFECTS)**.
2. NAPROSYN, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. For patients who require the use of an NSAID, coadministration with 15 mg of PREVACID Delayed-Release Capsules has been proven effective to reduce the risk of NSAID-associated gastric ulcers in patients with a previous history of documented gastric ulcers (see **CLINICAL STUDIES, Risk Reduction of NSAID-Associated Gastric Ulcer(s)**).
Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS, GI Effects - Risk of Ulceration, Bleeding, and Perforation**).
3. NAPROSYN, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalizations and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.
4. Patients should promptly report signs or symptoms of unexplained weight gain or edema to their physicians.
5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
6. Patients should be informed of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see **WARNINGS, Anaphylactoid Reactions).**
7. In late pregnancy, as with other NSAIDs, NAPROSYN should be avoided because it may cause premature closure of the ductus arteriosus.
8. Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo, or depression during therapy with naproxen.

Laboratory Tests

NAPROSYN
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, PREVACID NapraPAC should be discontinued.

Drug Interactions

NAPROSYN

ACE-inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE)-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Antacids and Sucralfate
Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen.

Aspirin
When naproxen as NAPROSYN is administered with aspirin, its protein binding is reduced, although the clearance of free NAPROSYN is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and aspirin is not generally recommended because of the potential of increased adverse effects.

Cholestyramine
As with other NSAIDs, concomitant administration of cholestyramine can delay the absorption of naproxen.

Diuretics
Clinical studies, as well as postmarketing observations, have shown that NAPROSYN can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see **WARNINGS: Renal Effects**), as well as to assure diuretic efficacy.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Naproxen and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

No significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants. However, caution is advised since interactions have been seen with other NSAIDs of this class. The free fraction of warfarin may increase substantially in some subjects and naproxen interferes with platelet function.

Selective Serotonin Reuptake Inhibitors (SSRIs)
There is an increased risk of GI bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs. Caution should be used when NSAIDs are administered concomitantly with SSRIs.

Other Information Concerning Drug Interactions
Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide, or sulphonylurea should be observed for adjustment of dose if required.

Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

PREVACID
PREVACID causes long-lasting inhibition of gastric acid secretion. PREVACID substantially decreases the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, PREVACID, or other proton pump inhibitors, should not be co-administered with atazanavir.

It is theoretically possible that PREVACID may also interfere with the absorption of other drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, digoxin).

PREVACID is metabolized through the cytochrome P_{450} system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that PREVACID does not have clinically significant interactions with other drugs metabolized by the cytochrome P_{450} system, such as warfarin, antipyrine, indomethacin, ibuprofen, phenytoin, propranolol, prednisone, diazepam, or clarithromycin in healthy subjects. These compounds are metabolized through various cytochrome P_{450} isozymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A.

When PREVACID was administered concomitantly with theophylline (CYP1A2, CYP3A), a minor increase (10%) in the clearance of theophylline was seen. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when PREVACID is started or stopped to ensure clinically effective blood levels.

In a study of healthy subjects, neither the pharmacokinetics of warfarin enantiomers nor prothrombin time were affected following single or multiple 60 mg doses of lansoprazole. However, there have been reports of increased International Normalized Ratio (INR) and prothrombin time in patients receiving proton pump inhibitors, including PREVACID, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

In an open-label, single-arm, eight-day, pharmacokinetic study of 28 adult rheumatoid arthritis patients (who required the chronic use of 7.5 to 15 mg of methotrexate given weekly), administration of 7 days of naproxen 500 mg BID and PREVACID 30 mg daily had no effect on the pharmacokinetics of methotrexate and 7-hydroxymethotrexate. While this study was not designed to assess the safety of this combination of drugs, no major adverse events were noted.

PREVACID has also been shown to have no clinically significant interaction with amoxicillin.

In a single-dose crossover study examining PREVACID 30 mg and omeprazole 20 mg each administered alone and concomitantly with sucralfate 1 gram, absorption of the proton pump inhibitors was delayed and their bioavailability was reduced by 17% and 16%, respectively, when administered concomitantly with sucralfate. Therefore, proton pump inhibitors should be taken at least 30 minutes prior to sucralfate. In clinical trials, antacids were administered concomitantly with PREVACID and there was no evidence of a change in the efficacy of PREVACID.

Drug/Laboratory Test Interactions

NAPROSYN
Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined.

The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Carcinogenesis, Mutagenesis, Impairment of Fertility

NAPROSYN
A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg per kg per day (50, 100, and 150 mg per m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorigenicity was found.

PREVACID
In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with oral lansoprazole doses of 5 to 150 mg per kg per day – about 1 to 40 times the exposure on a body surface (mg per m^2) basis of a 50-kg person of average height [1.46 m^2 body surface area (BSA)] given the recommended human dose of 30 mg per day (22.2 mg per m^2). Lansoprazole produced dose-related gastric enterochromaffin-like (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day (4 to 40 times the recommended human dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat. In addition, in a one-year toxicity study, testicular interstitial cell adenoma occurred in 1 of 30 rats treated with 50 mg per kg per day of lansoprazole (13 times the recommended human dose based on BSA).

In a 24-month carcinogenicity study, CD-1 mice were treated with oral lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg per kg per day (40 to 80 times the recommended human dose based on BSA) and female mice treated with 150 to 600 mg per kg per day (20 to 80 times the recommended human dose based on BSA) exceeded the ranges of

background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human dose based on BSA).

Lansoprazole was not genotoxic in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test, or the rat bone marrow cell chromosomal aberration test. It was positive in *in vitro* human lymphocyte chromosomal aberration assays.

Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

Pregnancy

Teratogenic Effects
Pregnancy Category C

PREVACID NapraPAC
There are no adequate and well-controlled studies of PREVACID NapraPAC in pregnant women. Because animal reproduction studies are not always predictive of human response, PREVACID NapraPAC should not be used during pregnancy unless clearly needed.

NAPROSYN
Reproduction studies have been performed in rats at 20 mg per kg per day (125 mg per m^2 per day, 0.23 times the human systemic exposure), rabbits at 20 mg per kg per day (220 mg per m^2 per day, 0.27 times the human systemic exposure), and mice at 170 mg per kg per day (510 mg per m^2 per day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due the drug. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. NAPROSYN should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

PREVACID
Teratology studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg per kg per day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg per kg per day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

Nonteratogenic Effects

NAPROSYN
There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. Naproxen-containing products are not recommended in labor and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage. The effects of PREVACID NapraPAC on labor and delivery in pregnant women are unknown.

Nursing Mothers

PREVACID NapraPAC
No PREVACID NapraPAC studies were conducted in nursing mothers. Since prostaglandin-inhibiting drugs (including NAPROSYN) may have adverse effects on neonates, the use of PREVACID NapraPAC in nursing mothers should be avoided.

NAPROSYN
The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

PREVACID
Lansoprazole or its metabolites are excreted in the milk of rats. It is not known whether lansoprazole is excreted in human milk. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions in nursing infants from lansoprazole, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue lansoprazole, taking into account the importance of lansoprazole to the mother.

Pediatric Use

PREVACID NapraPAC
The safety and effectiveness of PREVACID NapraPAC in pediatric patients have not been established.

Geriatric Use

NAPROSYN
Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of NSAIDs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population (see **WARNINGS, GI Effects – Risk of Ulceration, Bleeding, and Perforation**).

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of NSAIDs (see **WARNINGS, Renal Effects**).

PREVACID
The incidence rates of PREVACID-associated adverse events and laboratory test abnormalities are similar to those seen in younger patients. For geriatric patients, dosage and administration of PREVACID need not be altered.

Use in Women

PREVACID
Over 4,000 women were treated with PREVACID. Ulcer healing rates in females were similar to those in males. The incidence rates of adverse events in females were similar to those seen in males.

ADVERSE REACTIONS

NAPROSYN
Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis in controlled NAPROSYN trials are listed below. In general, reactions in patients treated chronically with NAPROSYN were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea. The most frequent complaints reported related to the GI tract.
A clinical study found GI reactions to be more frequent and more severe in rheumatoid arthritis patients taking daily doses of 1500 mg naproxen compared to those taking 750 mg naproxen (see **CLINICAL PHARMACOLOGY**).
In controlled clinical naproxen trials with about 80 pediatric patients and in well-monitored, open-label naproxen studies with about 400 pediatric patients with juvenile arthritis treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of GI and central nervous system reactions were about the same, and the incidence of other reactions were lower in pediatric patients than in adults.
In patients taking naproxen in clinical trials, the most frequently reported adverse experiences in approximately 1% to 10% of patients are:

GI Experiences, including: heartburn[1], abdominal pain[1], nausea[1], constipation[1], diarrhea, dyspepsia, stomatitis

Central Nervous System: headache[1], dizziness[1], drowsiness[1], lightheadedness, vertigo

Dermatologic: pruritus (itching)[1], skin eruptions[1], ecchymoses[1], sweating, purpura

Special Senses: tinnitus[1], visual disturbances, hearing disturbances

Cardiovascular: edema[1], palpitations

General: dyspnea[1], thirst
In patients taking NSAIDs, the following adverse experiences have also been reported in approximately 1% to 10% of patients.

GI Experiences, including: flatulence, gross bleeding/perforation, GI ulcers (gastric/duodenal), vomiting
General: abnormal renal function, anemia, elevated liver enzymes, increased bleeding time, rashes
The following are additional adverse experiences reported in less than 1% of patients taking naproxen during clinical trials and through postmarketing reports. Those adverse reactions observed through postmarketing reports are italicized.
Body as a Whole: *anaphylactoid reactions, angioneurotic edema, menstrual disorders, pyrexia (chills and fever)*
Cardiovascular: *congestive heart failure, vasculitis, hypertension, pulmonary edema*
GI: GI bleeding and/or *perforation, hematemesis,* pancreatitis, vomiting, *colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic GI ulceration, ulcerative stomatitis, esophagitis, peptic ulceration*
Hepatobiliary: jaundice, *abnormal liver function tests, hepatitis (some cases have been fatal)*
Hemic and Lymphatic: *eosinophilia, leucopenia,* melena, thrombocytopenia, agranulocytosis, *granulocytopenia, hemolytic anemia, aplastic anemia*
Metabolic and Nutritional: *hyperglycemia, hypoglycemia*
Nervous System: inability to concentrate, *depression, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, convulsions*
Respiratory: *eosinophilic pneumonitis, asthma*
Dermatologic: *alopecia, urticaria,* skin rashes, *toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, including Stevens-Johnson syndrome, photosensitive dermatitis, photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.*
Special Senses: *hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema*
Urogenital: *glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine*
Reproduction (female): *infertility*
In patients taking NSAIDs, the following adverse experiences have also been reported in less than 1% of patients:
Body as a Whole: fever, infection, sepsis, anaphylactic reactions, appetite changes, death
Cardiovascular: hypertension, tachycardia, syncope, arrhythmia, hypotension, myocardial infarction
GI: dry mouth, esophagitis, gastric/peptic ulcers, gastritis, glossitis, eructation
Hepatobiliary: hepatitis, liver failure
Hemic and Lymphatic: rectal bleeding, lymphadenopathy, pancytopenia
Metabolic and Nutritional: weight changes
Nervous System: anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, tremors, convulsions, coma, hallucinations
Respiratory: asthma, respiratory depression, pneumonia
Dermatologic: exfoliative dermatitis
Special Senses: blurred vision, conjunctivitis
Urogenital: cystitis, dysuria, oliguria/polyuria, proteinuria

1Incidence of reported reaction between 3% and 9%. Those reactions occurring in less than 3% of the patients are unmarked.

PREVACID

Clinical
Worldwide, over 10,000 patients have been treated with PREVACID in Phase 2 or Phase 3 clinical trials involving various dosages and durations of treatment. The adverse reaction profiles for PREVACID Delayed-Release Capsules and PREVACID for Delayed-Release Oral Suspension are similar. In general, PREVACID treatment has been well-tolerated in both short-term and long-term trials.

The following adverse events were reported by the treating physician to have a possible or probable relationship to drug in 1% or more of PREVACID-treated patients and occurred at a greater rate in PREVACID-treated patients than placebo-treated patients in Table 4.

Table 4: Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled PREVACID Studies

Body System/Adverse Event	PREVACID (N= 2768) %	Placebo (N= 1023) %
Body as a Whole		
Abdominal Pain	2.1	1.2
Digestive System		
Constipation	1.0	0.4
Diarrhea	3.8	2.3

Nausea	1.3	1.2

Headache was also seen at greater than 1% incidence but was more common on placebo. The incidence of diarrhea was similar between patients who received placebo and patients who received 15 mg and 30 mg of PREVACID, but higher in the patients who received 60 mg of PREVACID (2.9%, 1.4%, 4.2%, and 7.4%, respectively).

The most commonly reported possibly or probably treatment-related adverse event during maintenance therapy was diarrhea.

In the risk reduction study of PREVACID for NSAID-associated gastric ulcers, the incidence of diarrhea for patients treated with PREVACID, misoprostol, and placebo was 5%, 22%, and 3%, respectively.

Another study for the same indication, where patients took either a COX-2 inhibitor or lansoprazole and naproxen, demonstrated that the safety profile was similar to the prior study. Additional events from this study not previously observed in other clinical trials with PREVACID included contusion, duodenitis, epigastric discomfort, esophageal disorder, fatigue, hunger, hiatal hernia, hoarseness, impaired gastric emptying, metaplasia, and renal impairment.

Additional adverse experiences occurring in less than 1% of patients or subjects who received PREVACID in domestic trials are shown below:

Body as a Whole – abdomen enlarged, allergic reaction, asthenia, back pain, candidiasis, carcinoma, chest pain (not otherwise specified), chills, edema, fever, flu syndrome, halitosis, infection (not otherwise specified), malaise, neck pain, neck rigidity, pain, pelvic pain; *Cardiovascular System* - angina, arrhythmia, bradycardia, cerebrovascular accident/cerebral infarction, hypertension/ hypotension, migraine, myocardial infarction, palpitations, shock (circulatory failure), syncope, tachycardia, vasodilation; *Digestive System* – abnormal stools, anorexia, bezoar, cardiospasm, cholelithiasis, colitis, dry mouth, dyspepsia, dysphagia, enteritis, eructation, esophageal stenosis, esophageal ulcer, esophagitis, fecal discoloration, flatulence, gastric nodules/fundic gland polyps, gastritis, gastroenteritis, GI anomaly, GI disorder, GI hemorrhage, glossitis, gum hemorrhage, hematemesis, increased appetite, increased salivation, melena, mouth ulceration, nausea and vomiting, nausea and vomiting and diarrhea, gastrointestinal moniliasis, rectal disorder, rectal hemorrhage, stomatitis, tenesmus, thirst, tongue disorder, ulcerative colitis, ulcerative stomatitis; *Endocrine System* - diabetes mellitus, goiter, hypothyroidism; *Hemic and Lymphatic System* - anemia, hemolysis, lymphadenopathy; *Metabolic and Nutritional Disorders* - avitaminosis, gout, dehydration, hyperglycemia /hypoglycemia, peripheral edema, weight gain/ loss; *Musculoskeletal System* - arthralgia, arthritis, bone disorder, joint disorder, leg cramps, musculoskeletal pain, myalgia, myasthenia, ptosis, synovitis; *Nervous System* - abnormal dreams, agitation, amnesia, anxiety, apathy, confusion, convulsion, dementia, depersonalization, depression, diplopia, dizziness, emotional lability, hallucinations, hemiplegia, hostility aggravated, hyperkinesia, hypertonia, hypesthesia, insomnia, libido decreased /increased, nervousness, neurosis, paresthesia, sleep disorder, somnolence, thinking abnormality, tremor, vertigo; *Respiratory System* - asthma, bronchitis, cough increased, dyspnea, epistaxis, hemoptysis, hiccup, laryngeal neoplasia, lung fibrosis, pharyngitis, pleural disorder, pneumonia, respiratory disorder, upper respiratory inflammation/infection, rhinitis, sinusitis, stridor; *Skin and Appendages* - acne, alopecia, contact dermatitis, dry skin, fixed eruption, hair disorder, maculopapular rash, nail disorder, pruritus, rash, skin carcinoma, skin disorder, sweating, urticaria; *Special Senses* - abnormal vision, amblyopia, blepharitis, blurred vision, cataract, conjunctivitis, deafness, dry eyes, ear/eye disorder, eye pain, glaucoma, otitis media, parosmia, photophobia, retinal degeneration/disorder, taste loss, taste perversion, tinnitus, visual field defect; *Urogenital System* - abnormal menses, breast enlargement, breast pain, breast tenderness, dysmenorrhea, dysuria, gynecomastia, impotence, kidney calculus, kidney pain, leukorrhea, menorrhagia, menstrual disorder, penis disorder, polyuria, testis disorder, urethral pain, urinary frequency, urinary retention, urinary tract infection, urinary urgency, urination impaired, vaginitis.

Postmarketing
Additional adverse experiences have been reported since PREVACID has been marketed. The majority of these cases are foreign-sourced and a relationship to PREVACID has not been established. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events are listed below by COSTART body system.

Body as a Whole - anaphylactic/anaphylactoid reactions; *Digestive System* - hepatotoxicity, pancreatitis, vomiting; *Hemic and Lymphatic System* - agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and thrombotic thrombocytopenic purpura; *Musculoskeletal System* – myositis; *Skin and Appendages* – severe dermatologic reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal); *Special Senses* - speech disorder; *Urogenital System* – interstitial nephritis, urinary retention.

Laboratory Values
The following changes in laboratory parameters in patients who received PREVACID were reported as adverse events:

Abnormal liver function tests, increased SGOT (AST), increased SGPT (ALT), increased creatinine, increased alkaline phosphatase, increased globulins, increased GGTP, increased/decreased/abnormal WBC, abnormal AG ratio, abnormal RBC, bilirubinemia, blood potassium increased, blood urea increased, crystal urine present, eosinophilia, hemoglobin decreased hyperlipemia, increased/

decreased electrolytes, increased/decreased cholesterol, increased glucocorticoids, increased LDH, increased/decreased/abnormal platelets, increased gastrin levels and positive fecal occult blood. Urine abnormalities such as albuminuria, glycosuria, and hematuria were also reported. Additional isolated laboratory abnormalities were reported.

In the placebo controlled studies, when SGOT (AST) and SGPT (ALT) were evaluated, 0.4% (4 of 978) and 0.4% (11 of 2677) patients, who received placebo and PREVACID, respectively, had enzyme elevations greater than three times the upper limit of normal range at the final treatment visit. None of these patients who received PREVACID reported jaundice at any time during the study.

OVERDOSAGE

PREVACID NapraPAC

In case of a PREVACID NapraPAC overdose, patients should contact a physician, poison control center, or emergency room.
There are no data suggesting increased toxicity of the combination of NAPROSYN and PREVACID compared with the individual components.
To avoid exceeding the recommended doses of naproxen, do not use other naproxen-containing products (including NAPROSYN, ANAPROX/ANAPROX-DS, ALEVE, or naproxen sodium) with PREVACID NapraPAC.

NAPROSYN

Symptoms and Signs
Significant naproxen overdosage may be characterized by lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation, or vomiting. GI bleeding can occur. Hypertension, acute renal failure, respiratory depression, and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.
A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters, and greater than 1000 mg/kg in dogs.

Treatment
Patients should be managed by symptomatic and supportive care following a NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. Emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 g per kg in children) and/or osmotic cathartic may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose. Forced diuresis, alkalinization of urine, or hemoperfusion may not be useful due to high protein binding.

PREVACID

PREVACID is not removed from the circulation by hemodialysis. In one reported overdose, a patient consumed 600 mg of PREVACID with no adverse reaction.
Oral PREVACID doses up to 5000 mg per kg in rats (approximately 1300 times the 30 mg human dose based on BSA) and in mice (about 675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

DOSAGE AND ADMINISTRATION

Carefully consider the potential benefits and risks of PREVACID NapraPAC and other treatment options before deciding to use PREVACID NapraPAC. Use the lowest effective NAPROSYN dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).
The recommended PREVACID NapraPAC dose for the risk reduction of NSAID-associated gastric ulcers – in adult patients with a history of a documented gastric ulcer who require the use of an NSAID – for the treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and/or ankylosing spondylitis is the following:
PREVACID NapraPAC 500: One 15 mg PREVACID capsule once daily and one 500 mg NAPROSYN tablet BID (1000 mg of NAPROSYN daily).
In the morning before eating, take the PREVACID capsule and one NAPROSYN tablet with a glass of water. In the evening, take the second NAPROSYN tablet with a glass of water. PREVACID Delayed-Release Capsules should be swallowed whole; they should not be chewed or crushed.
After observing the response to initial therapy with PREVACID NapraPAC, the NAPROSYN dose and frequency should be adjusted to suit an individual patient's needs. Controlled studies of PREVACID NapraPAC did not extend beyond 12 weeks.
Renal insufficiency patients and geriatric patients do not require adjustment of the 15 mg PREVACID component of PREVACID NapraPAC, however dose adjustment should be considered for patients with severe liver disease.
Dose adjustment for the NAPROSYN component of PREVACID NapraPAC should be considered for geriatric patients and patients with liver disease. NAPROSYN-containing products are not recommended for use in patients with moderate to severe and severe

renal impairment (creatinine clearance less than 30 mL per minute) (see **WARNINGS, Renal Effects; PRECAUTIONS, Hepatic Effects;** and **PRECAUTIONS, Geriatric Use**).

HOW SUPPLIED

PREVACID NapraPAC 500 is supplied as a weekly blister card packaged as a monthly (28 days) course of therapy. Each weekly blister card contains:

PREVACID

- Seven opaque, hard gelatin, pink and green PREVACID 15 mg capsules, with "TAP" and "PREVACID 15" imprinted on the capsules.

NAPROSYN

- Fourteen yellow, capsule-shaped tablets, engraved with NPR LE 500 on one side and scored on the other.

NDC 64764-546-07 Weekly Blister Card, 500 mg
NDC 64764-546-30 One Month Administration Pack, 500 mg

Storage

Protect from light and moisture.
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]
Store and dispense in original container.

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Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

(See the end of this Medication Guide for a list of prescription NSAID medicines.)

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called "corticosteroids" and "anticoagulants"
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment

• for the shortest time needed

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?
NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as:
• different types of arthritis

• menstrual cramps and other types of short-term pain

Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)?
Do not take an NSAID medicine:
• if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine

• for pain right before or after heart bypass surgery

Tell your healthcare provider:
• about all of your medical conditions.

• about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Keep a list of your medicines to show to your healthcare provider and pharmacist.**

• if you are pregnant. **NSAID medicines should not be used by pregnant women late in their pregnancy.**

• if you are breastfeeding. **Talk to your doctor.**

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs *(*NSAIDs)?

Serious side effects include:	**Other side effects include:**
• heart attack	• stomach pain
• stroke	• constipation
• high blood pressure	• diarrhea
• heart failure from body swelling (fluid retention)	• gas
• kidney problems including kidney failure	• heartburn
• bleeding and ulcers in the stomach and intestine	• nausea
• low red blood cells (anemia)	• vomiting
• life-threatening skin reactions	• dizziness
• life-threatening allergic reactions	
• liver problems including liver failure	
• asthma attacks in people who have asthma	

Get emergency help right away if you have any of the following symptoms:
• shortness of breath or trouble breathing

• chest pain

• weakness in one part or side of your body

- slurred speech
- swelling of the face or throat

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:
- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

Other information about Non-Steroidal Anti-Inflammatory Drugs *(*NSAIDs)
- Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Flector, Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbirofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, PREVACID NapraPAC (PREVACID copackaged with NAPROSYN)
Oxaprozin	Daypro
Piroxicam	Feldene

Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

*****Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAID, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

PREVACID® NapraPAC® (pr#v # s#d napr# pak)
(lansoprazole delayed release capsules and naproxen tablets kit)

What is PREVACID® NapraPAC®?

PREVACID NapraPAC contains two medicines:

1. PREVACID® (lansoprazole) Delayed-Release Capsules. PREVACID is a proton pump inhibitor (a medicine that reduces stomach acid); and

2. NAPROSYN® (naproxen) Tablets. NAPROSYN is a nonsteroidal anti-inflammatory drug (NSAID). Please read the above information regarding the benefits and risks of NSAIDs, including NAPROSYN.

PREVACID NapraPAC is used to lower the chance of getting another stomach ulcer in adult patients who have had stomach ulcers and who need to take an NSAID to treat the signs and symptoms of rheumatoid arthritis, osteoarthritis, and/or ankylosing spondylitis. It is not known if PREVACID NapraPAC lowers the risk of ulcers of the intestines or if PREVACID NapraPAC reduces the risk of bleeding from stomach ulcers and ulcers of the intestines.

PREVACID NapraPAC comes in the following strength:

One PREVACID 15 mg capsule and two NAPROSYN 500 mg tablets

The lowest possible dose for the shortest time possible should be prescribed to treat your condition.

PREVACID NapraPAC has not been studied in children.

Can I take other medicines with PREVACID NapraPAC?

Tell your doctor about all of the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. Both of the medicines in PREVACID NapraPAC can affect other medicines you take and sometimes cause serious side effects. Especially, tell your doctor if you take:

- blood pressure medicines
- aspirin
- water pills (diuretics)
- lithium
- methotrexate
- warfarin (Coumadin)
- theophylline
- sucralfate
- ketoconazole
- ampicillin
- iron salts
- digoxin

How should I take PREVACID NapraPAC?

- **In the morning before eating,** take one PREVACID capsule and one NAPROSYN tablet with a glass of water. **In the evening,** take the second NAPROSYN tablet with a glass of water.
- Swallow PREVACID capsules whole. Do not crush or chew PREVACID capsules. If you take sucralfate, PREVACID should be taken 30 minutes before sucralfate.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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